UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,564	11/07/2000	Florian Kern	KREISLER1089	5234

27384 7590 11/19/2010

Briscoe, Kurt G.
Norris McLaughlin & Marcus, PA
875 Third Avenue, 8th Floor
New York, NY 10022

EXAMINER	
ZEMAN, ROBERT A	
ART UNIT	PAPER NUMBER
1645	
MAIL DATE	DELIVERY MODE
11/19/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/600,564	KERN ET AL.	
	Examiner	Art Unit	
	ROBERT A. ZEMAN	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-26* is/are pending in the application.

4a) Of the above claim(s) *22-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12-22-2009 has been entered.

The amendment and response filed on 12-22-2009 are acknowledged. Claim 27 has been canceled. Claims 14-26 are pending. Claims 22-26 remain withdrawn from consideration as being drawn to non-elected invention(s). Claims 14-21 are currently under examination.

Declaration

The declaration by Florian Kern filed on 12-22-2009 has been fully considered.

Claim Objections Withdrawn

The objection to claim 27 under 37 CFR 1.75 as being a substantial duplicate of claim 14 is withdrawn. Cancellation of said claim has rendered the objection moot.

Claim Rejections Withdrawn

The rejection of claims 14-21 under 35 U.S.C. 103(a) as being unpatentable over Yanagisawa et al. (International Immunology, 1997, Vol. 9 No. 2, pages 227-237) and Picker et

al. (Blood, 1995, Vol. 86 No. 4, pages 1408-1419 -- IDS) is withdrawn in lieu of the rejection set forth below.

New Claim Objections

Claim 14 is objected to as its claim language is confusing. It is suggest that the portion of the claim characterizing the incubation time be incorporated into step d).

Claim Rejections Maintained

35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The rejection of claims 14 and 16-21under 35 U.S.C. 102(a) as being anticipated by Yanagisawa et al. (International Immunology, 1997, Vol. 9 No. 2, pages 227-237) is maintained for reasons of record. Applicant's arguments were found persuasive with regard to claim 15. The cancellation of claim 27 has rendered the rejection of said claim moot.

Applicant argues:

1. Specific elimination occurs following specific activation and is based on the deprivation of nutrients and growth factors to the "non-activated" cells by the "activated" cells.

2. Basing a rejection the based on claim language drawn to "particular" T cells is a semantic game and not reason for rejecting a claim.

3. That since the time period specified by applicant in his method is 4 times shorter than the shortest time period specified by Yanagisawa et al. and because of the obvious advantage of performing the entire procedure within one working day; applicant has demonstrated a significant and useful difference between his invention and the process of Yanagisawa et al.

4. No activation marker is measured by Yanagisawa et al.

5. Yanagisawa et al. only allows mapping of the epitopes at a rough population level not at the single cell level.

Applicant's arguments and the Declaration by Florian Kern have been fully considered and deemed non-persuasive.

With regard to Point 1, while Applicant is correct in his assertion that the activation of a given T cells will lead its increased consumption of nutrients due to proliferation, his assertion that this increased consumption leads to the specific starvation of non-activated clones is erroneous. Contrary to Applicant's assertion, the effects of nutrient deprivation would be applied equally to all cells within a given "culture". Over time any the percentage of proliferating cells within said culture would increase due to their expanding numbers. However, the sheer number of cells eliminated due to "starvation" would be greater in the stimulated population as overall numbers would be greater. Consequently, there is no specific elimination of "non-stimulated" T-cells. Finally, it should be noted that both stimulated and non-stimulated cells would be subject to the effects of nutrient deprivation at the same time.

With regard to Point 2, Applicant's arguments are not germane as the instant claims do not contain claim language drawn to "particular" T cells.

With regard to Point 3 Applicant is reminded that the instant claims recited no definite time periods. The independent claims define the incubation time as a duration "sufficiently long so that the protein fragment or fragments are sufficiently taken up by the major histocompatibility antigen (MHC) molecules said taking up being sufficient when an unambiguous identification of stimulated T cells is possible" and "… sufficiently short so that selection and proliferation accompanied by the specific elimination of stimulated T cells do not occur". This time period would necessarily vary from cell population to cell population. More importantly, the upper end of the claimed "range" is defined by the "the specific elimination of stimulated T cells" not occurring. It is deemed that since the cellular functions and surface markers of the stimulated cells are effectively measured by Yanagisawa et al., said cells have not be "eliminated". Moreover, contrary to Applicant's assertion, the instant claims do not require the claimed method to be performed "within one working day".

With regard to Point 4, Yanagisawa et al. disclose the measurement of multiple T cell markers including CD4 (see pages 228-229).

With regard to Point 5, flow cytometry measures each cell individually. Moreover, Applicant is reminded that the requirement for the measurement of activation markers to be on the individual cell level is only present in claim 15.

The instant claims are drawn to methods for identification of T-cell stimulating protein fragments comprising the following steps:

- detecting an amino acid sequence of an antigen;

- subdividing the amino acid sequence into fragments;
- providing (synthesizing) at least one protein fragment;
- incubating a suspension containing T-cells with the protein fragment;
- identifying an induced T-cell cytokine or activation of a marker by flow cytometry;
- assigning experimental runs in which T-cells have been stimulated and the stimulation has been recognized by a T-cell cytokine or an activation marker.

The aforementioned method also requires that the incubation time of the protein fragment(s) with cell suspension containing T cells be of a duration "sufficiently long so that the protein fragment or fragments are sufficiently taken up by the major histocompatibility antigen (MHC) molecules said taking up being sufficient when an unambiguous identification of stimulated T cells is possible" and "… sufficiently short so that selection and proliferation accompanied by the elimination of stimulated T cells do not occur".

As outlined previously, Yanagisawa et al. disclose methods of mapping T cell epitopes on mycobacterial antigens by measuring the usage of the TCR β chair repertoire by flow cytometry. Yanagisawa et al. further disclose the addition of 15-mer peptides, overlapping by five amino acids, covering the complete MPT59 protein to T cell suspensions prepared from the inguinal lymph nodes from various strains of mice (see page 228). The expression of cell surface antigens (including TCR $V_{\beta)}$ was measured before and after culturing (see page 229).

With regard to the limitation that the incubation time be sufficiently short so that selection, proliferation and the specific elimination of stimulated T cells does not occur, it is deemed, in absence to evidence to the contrary, that since the active expression of cell surface markers and are measured on the stimulated T cells, said cells could not have been eliminated.

New Grounds of Rejection

35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The steps recited in claim 14 are confusing. It is unclear how one can perform step b) prior to the synthesizing of antigen fragments or the cleaving of the antigen as recited in claim c). Consequently, it is impossible to determine the metes and bounds of the claimed invention.

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Picker et al. (Blood, 1995, Vol. 86 No. 4, pages 1408-1419 -- IDS) and Yanagisawa et al. (International Immunology, 1997, Vol. 9 No. 2, pages 227-237).

The instant claims are drawn to methods for identification of T-cell stimulating protein fragments comprising the following steps:

- detecting an amino acid sequence of an antigen;
- subdividing the amino acid sequence into fragments;
- providing (synthesizing) at least one protein fragment;
- incubating a suspension containing T-cells with the protein fragment;
- identifying an induced T-cell cytokine or activation of a marker by flow cytometry;
- assigning experimental runs in which T-cells have been stimulated and the stimulation has been recognized by a T-cell cytokine or an activation marker.

The aforementioned method also requires that the incubation time of the protein fragment(s) with cell suspension containing T cells be of a duration "sufficiently long so that the protein fragment or fragments are sufficiently taken up by the major histocompatibility antigen (MHC) molecules said taking up being sufficient when an unambiguous identification of stimulated T cells is possible" and "… sufficiently short so that selection and proliferation accompanied by the elimination of stimulated T cells do not occur".

Picker et al. disclose a multi-parameter flow cytometric assay that allows the simultaneous determination of an individual T cell's ability to produce multiple cytokines and its phenotypes after a short (4 to 8 hours) *in vitro* incubation with an activating stimulus (antigen) [see abstract]. Picker et al. further disclose that said T cells could be contained in peripheral blood samples (see page 1409).

Picker et al. differs from the instant invention in that they do not disclose the use of their multi-parameter flow cytometric assay to identify T-cell stimulating antigen fragments.

Yanagisawa et al. disclose methods of mapping T cell epitopes on mycobacterial antigens by measuring the usage of the TCR β chair repertoire by flow cytometry. Yanagisawa et al. further disclose the addition of 15-mer peptides, overlapping by five amino acids, covering the complete MPT59 protein to T cell suspensions prepared from the inguinal lymph nodes from various strains of mice (see page 228). The expression of cell surface antigens (including TCR $V_{\beta)}$ was measure before and after culturing. Additionally the production of IFN-γ, IL-10, IL-5 and IL-4 was measured (see page 229).

It would have been obvious for one of ordinary skill in the art at the time of the invention to use the flow cytometry method of Picker et al. in the epitope mapping method of Yanagisawa et al. in order to take advantage rapid ability to determine the functional potential (i.e. response) of phenotypically distinct T cell subsets.

One would have had a reasonable expectation of success since Picker et al. disclose that the "simplicity and rapidity" of their detection technique coupled with the widespread availability of flow cytometers and T cell phenotyping antibodies suggest that their technique could be broadly applicable to the evaluation of immune status (see page 1418). Moreover, given

that the use of flow cytometry to measure cytokine levels is well known in the art (as acknowledged by Applicant) yielding predictable results, it is obvious for the skilled artisan to use flow cytometry in the methods of Yanagisawa et al. (see *KSR International Co. v. Teleflex Inc.*, No. 04-1350 [U.S. Apr. 30, 2007]).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT A. ZEMAN whose telephone number is (571)272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m. .

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert A. Zeman/
Primary Examiner, Art Unit 1645
November 17, 2010